Kidney International, Vol. 39 (1991), pp. 1193–1205

CLINICAL INVESTIGATION

Diet, vitamin D and vertebral mineral density in hypercalciuric calcium stone formers

PIERRE BATAILLE, JEAN MICHEL ACHARD, ALBERT FOURNIER, BERNARD BOUDAILLIEZ, PIERRE FRANÇOIS WESTEEL, NAJEH EL ESPER, CATHERINE BERGOT, IVO JANS, JEAN DANIEL LALAU, JACQUES PETIT, GHYSLAINE HENON, MARIE ANNE LAVAL JEANTET, ROGER BOUILLON, and JEAN LUC SEBERT

Service de Néphrologie, Centre Hospitalier, 62100 Boulogne; Service de Néphrologie, Urologie, Endocrinologie, Rhumatologie et Pédiatrie du CHU, Amiens; Service de Radiologie du CHU St Louis, Paris; Laboratoire de Biochimie du CHU, Amiens; and Laboratory of Experimental Medicine, St Rafael Clinic, Leuven; France

Diet, vitamin D and vertebral mineral density in hypercalciuric calcium stone formers. To elucidate the pathophysiology of dietary calcium independent hypercalciuria, 42 calcium stone formers (Ca SF) were selected because they had on free diet a calciuria greater than 0.1 mmol/kg/day. For four days they were put on a diet restricted in calcium (Ca RD) by exclusion of the dairy products. They collected 24 hour urines on free diet and on day 4 of Ca RD as well as the two-hour fasting urines on the morning of the day 5 and the four-hour urines passed after an oral calcium load of 1 g, for measurement of creatinine, Ca, PO_4, urea and total hydroxyprolinuria (THP). On day 5 fasting plasma concentrations of Ca, PO_4, intact PTH, Gla protein, calcidiol and calcitriol were measured. The patients were firstly classified into dietary hypercalciuria (DH, 18 patients) and dietary calcium-independent hypercalciuria (IH, 24 patients) on the basis of the disappearance or not of hypercalciuria on Ca RD. Then the patients with IH were subclassified into absorptive hypercalciuria (AH) because of normal fasting calciuria (8 patients) and into fasting hypercalciuria (16 patients). Fasting hypercalciuric patients were subsequently divided according to the PTH levels into renal hypercalciuria (RH, 1 patient) with elevated fasting PTH becoming normal after the Ca load and undetermined hypercalciuria (UH, 15 patients) with normal PTH levels. Furthermore, their vertebral mineral density (VMD) was measured by quantitative computerized tomography which was normal in DH (91 ± 6% of the normal mean for age and sex) but was decreased in IH to 69 ± 4%. No difference in VMD was observed between AH and UH. Urinary excretions of urea, phosphate and THP was higher in IH than in DH and comparable in AH and UH. Sodium excretion Ca RD was the same in all groups and subgroups as well as the plasma parameters. Plasma calcitriol was increased in IH and DH comparatively to normal in spite of normal plasma calcidiol. Calciuria increase after oral calcium load, an index of Ca absorption, was higher in IH than in controls and comparable in IH and DH as well as in the three subgroups of IH. From these data and correlation studies in IH it is concluded: (1.) VMD is decreased in Ca stone formers with IH but not in those with DH, making the distinction of these two groups of hypercalciuria patients clinically relevant. (2.) The further distinction within IH of AH, RH and UH is not very justified, since RH is exceptional and VMD and other biochemical parameters (with the exception of those taken for subclassification) are not different between AH and UH. (3.) Since in IH, fasting hydroxyprolinuria and fasting calciuria were greater than in control, whereas plasma PTH concentrations were low to normal (with the exception of the case with RH), and fasting calciuria was correlated to fasting hydroxyprolinuria, it is suggested that a primary bone hyperresorption, and not a primary renal leak of calcium or a primary intestinal hyperabsorption, is the main cause of IH. (4.) IH is associated with higher urea excretion on free and Ca R diets than in controls, suggesting a higher protein intake of no dairy origin. This higher intake may favor bone resorption since fasting calciuria and hydroxyprolinuria are correlated to urea excretion. (5.) In IH, the positive correlations of calcitriol with VMD and calciuria increase after Ca oral load, and the negative one between calcitriol and fasting calciuria, suggest that calcitriol attenuates bone resorption by increasing calcium absorption. (6.) In IH, plasma calcitriol is correlated positively to calcidiol and negatively to plasma phosphate which remains in the normal range. Therefore, increased plasma calcitriol in IH may be explained by a hypersensitivity of 25 (OH) vitamin $D_{1\alpha}$ hydroxylase to PPO_4, making its synthesis dependent upon 25 (OH) D. (7.) Exclusion of dairy products might be deleterious for the skeleton in Ca stone formers. Restriction of protein intake of non-dairy origin should rather be advised.

Idiopathic calcium stone disease is a multifactorial disease and hypercalciuria, present in 30 to 60% of the patients, is its most frequent risk factor [1]. Hypercalciuria due to an excessive intake of calcium is called absorptive hypercalciuria type II or dietary hypercalciuria [2]. When hypercalciuria persists in spite of normal or restricted calcium intake it is usually called idiopathic hypercalciuria. The pathogenesis of this disorder is still highly controversial. Pak et al [2] classify idiopathic hypercalciuria into three distinct pathogenetic subtypes according to three independent, primary metabolic defects: (1) absorptive hypercalciuria type I when a primary intestinal hyperabsorption of calcium is involved; (2) absorptive hypercalciuria type III when a primary renal leak of phosphate is present inducing hypophosphatemia, and secondarily calcitriol-mediated intestinal hyperabsorption of calcium; (3) renal hypercalciuria when a primary renal leak of calcium is present inducing secondary hyperparathyroidism with calcitriol mediated hyperabsorption of calcium. According to Pak, "resorptive hypercalciuria," that is, a hypercalciuria due to primary bone hyperresorption, is always in relation to a nosologically well defined bone disease like primary hyperparathyroidism, Cushing's syndrome or hy-

Received for publication September 18, 1989
and in revised form November 21, 1990
Accepted for publication January 11, 1991

perthyroidism, the presence of which excludes the diagnosis of idiopathic hypercalciuria. Other authors do not agree, however, with such a clear-cut metabolic classification for various reasons:

(a) This classification does not take into account the dependence of idiopathic hypercalciuria on dietary factors other than the calcium intake, especially the intakes of sodium and protein, which now appear to be well established [3–5].

(b) The overprevalence of the absorptive hypercalciuria type I of Pak et al's definition (2/3 of the patients with idiopathic hypercalciuria) is in blatant contradiction with calcium balance data which show a negative balance in 2/3 of the patients [1, 6] [the average calcium balance for the hypercalciuric calcium-stone formers is -1.0 ± 2.7 mmol/day (-40 ± 108 mg/day), whereas it is $+0.7 \pm 2.4$ mmol/day (28 ± 96 mg/day) in healthy controls] [1].

(c) Primary disorders of the intestinal calcium absorption and tubular reabsorption of calcium or phosphate appear to be variously associated in the same patients, making their classification into distinct pathogenetic subtypes not always possible [5–7].

(d) The classification of Pak et al is not able to classify all patients, namely those with fasting hypercalciuria not related to a high sodium intake. Most of these patients don't have high plasma concentrations of PTH, but normal or low concentrations, which excludes the hypothesis of a renal hypercalciuria [8]. Since in these patients total hydroxyprolinuria is increased, a primary bone resorption not related to a defined nosological entity has been advocated [9].

To clarify the pathogenesis of idiopathic hypercalciuria, we selected 42 calcium stone formers with hypercalciuria on free diet. These patients were investigated by measuring their vertebral mineral density simultaneously with their urinary excretion of calcium, phosphate, sodium, urea and total hydroxyproline on free and calcium restricted diets and in fasting condition in order to assess the relationship of their calcium excretion with sodium and protein intake and bone catabolism. Plasma parameters of the mineral metabolism were measured to get some insight into the hormonal control of this metabolism.

Methods

Design of the biochemical evaluation of the patients

Forty-two calcium stone formers with normal renal function were selected because on free diet they had a calciuria higher than 4 mg/kg/day (>0.1 mmol/kg/day), normocalcemia, and no other clinical or biological evidence for sarcoidosis, lymphoma or complete distal renal tubular acidosis (normal plasma bicarbonate and potassium, fasting urinary pH ≤6.3). Review of their excretory urogram disclosed, however, three patients with an unequivocal pattern of medullary sponge kidney (MSK) according to the criteria given by Parks, Coe and Strauss [10], namely radial linear striations or cystic collections of contrast medium in the absence of concurrent obstruction of either kidney observed at least in half the papillae of both kidneys. For four days the 42 patients were put on a calcium restricted diet of about 400 mg by exclusion of all dairy products, while moderate sodium intake (no salt on the table) and exclusion of food rich in gelatine was prescribed. They were asked to collect their 24 hour urine on day 4 of this diet, as well as a fasting two-hour urine (7:00 to 9:00 a.m.) on the morning of day 5 after 12 hours of fasting. At 9 a.m. of this day they had their blood drawn and they were given an oral load of 1 g of elemental calcium (as gluconolactate and carbonate in 2 tablets of *Calcium Forte Sandoz*). Their urine was collected during the four following hours, and their blood was drawn again at 1 p.m.

Biochemical measurements

Plasma concentrations of the following parameters were measured: creatinine, calcium, phosphate, bicarbonate, protein, alkaline phosphatase by autoanalyzer techniques.

Bone Gla protein by radioimmunoassay with the CIS international kit was measured according to the method developed by Delmas et al [11].

Calcidiol was measured by a radio-competition assay [12] and calcitriol by a radioimmunoassay described by one of us [13].

Intact PTH by radioimmunoassay using the Nichols Institute kit according to the method developed by Kao et al was determined in serum samples [14].

In the 24-hour urine collected on free and calcium restricted diet, the following parameters were measured: creatinine, calcium, phosphate, urea, total hydroxyproline (THP) (the latter only on calcium restricted diet) by an autoanalyzer [15] On the fasting urines, creatinine, calcium and THP were measured. On the four hour urine following the calcium load, calcium and creatinine were measured again. All the urinary excretions have been reported by mmol of creatininuria to eliminate the urine sampling error.

Control values of the biochemical data

Control data for biochemical parameters were derived from different control populations but always explored in the same dietary conditions as the patients.

Normal values for calcium, phosphate, sodium and urea excretions as well as for plasma calcium, phosphate and protein were obtained in 41 healthy men and 21 healthy women in whom urolithiasis was excluded by X-rays and who had no clinical disorder affecting the calcium phosphate metabolism.

Control values for hydroxyprolinuria were obtained in 22 other healthy subjects studied after four days of Ca R diet and in fasting conditions. These controls were 15 men and 7 women with a mean age of 35 years.

Control values for serum PTH, plasma 25 (OH) vitamin D, plasma1,25 $(OH)_2$ vitamin D_3 were obtained in 12 controls (7 males, 5 females) without history of stone disease or disturbance of calcium metabolism. These control individuals had the same dietary conditions as the patients, namely, four days of Ca restricted diet with low gelatin intake. At odds with the patients, plasma samples of these controls were taken mainly in March for 10 of them, whereas they were taken throughout the year for the patients (5 times in summer, 4 times in autumn, 4 times in spring, 4 times in winter for the patients with dietary hypercalciuria and 10 times in summer, 5 times in autumn, 5 times in winter and 4 times in spring for the patients with idiopathic hypercalciuria).

Classification of the patients

Based on our own control data of calcium excretion on various diets and of fasting serum PTH concentrations, the

Table 1. Urine biochemical parameters according to the calcium diet

Calcium diet *N*	Urinary parameter *per mmol* U_{Cr}	Controls 61	Dietary hypercalciuria 18	Dietary calcium-independent hypercalciuria 24	Dietary calcium-independent hypercalciuria		
					Absorptive hypercalciuria type I 8	Renal hyper-calciuria 1	Undetermined hyper-calciuria 15
Free	U_{Ca}mmol	0.33 ± 0.02	0.55 ± 0.04[a3]	0.74 ± 0.04[b3,c3]	0.62 ± 0.04	0.86	0.79 ± 0.06
	U_{PO_4}mmol	1.9 ± 0.08	2.1 ± 0.1	2.3 ± 0.2[b2]	2.1 ± 0.1	1.74	2.5 ± 0.2
	U_{urea}mmol	26 ± 1	23 ± 1	27 ± 1[b1]	25 ± 1	22	28 ± 1
	U_{Na}mmol	10 ± 0.4	12 ± 1[a1]	12 ± 1[b3]	13 ± 1	11	12 ± 1
10 mmol/day	U_{Ca}mmol	0.21 ± 0.01	0.31 ± 0.02	0.62 ± 0.04[b3,c3]	0.47 ± 0.03	0.83	0.67 ± 0.04[d3]
	U_{PO_4}mmol	1.8 ± 0.05	1.9 ± 0.1	2.3 ± 0.2[b2,c2]	2.0 ± 0.1	2.5	2.4 ± 0.2
	U_{urea}mmol	23 ± 1	24 ± 1	28 ± 1[b3,c1]	26 ± 2	23	29 ± 2
	U_{Na}mmol	9 ± 0.5	9 ± 1	10 ± 2	12 ± 2	9	10 ± 1
	$U_{THP}\mu$mol	21 ± 1[e]	24 ± 2	32 ± 2[b3,c1]	27 ± 5	31	34 ± 3
Fasting	U_{Ca}mmol	0.16 ± 0.01	0.22 ± 0.02	0.44 ± 0.05[b3,c3]	0.22 ± 0.03	0.66	0.55 ± 0.06[d3]
	U_{PO_4}mmol	1.6 ± 0.2	1.6 ± 0.1	1.6 ± 1.2	1.8 ± 0.5	2.4	1.4 ± 2
	$U_{THP}\mu$mol	21 ± 1	24 ± 2	29 ± 4[b2]	24 ± 3	31	31 ± 4
After 25 mmol Ca load	U_{Ca}mmol	0.51 ± 0.03	0.67 ± 0.09	0.99 ± 0.05[b3]	0.79 ± 0.06	1.11	1.08 ± 0.07[d2]
	ΔU_{Ca}mmol	0.37 ± 0.03	0.47 ± 0.07	0.55 ± 0.05[b3]	0.57 ± 0.06[b1]	0.45	0.53 ± 0.08[b1]

Significance of the comparisons:
Controls versus dietary hypercalciuria: [a1] $P < 0.05$; [a2] $P < 0.02$; [a3] $P < 0.01$
Controls versus idiopathic hypercalciuria: [b1] $P < 0.05$; [b2] $P < 0.02$; [b3] $P < 0.01$
Dietary versus idiopathic hypercalciuria: [c1] $P < 0.05$; [c2] $P < 0.02$; [c3] $P < 0.01$
Absorptive I versus undetermined hypercalciuria: [d1] $P < 0.05$; [d2] $P < 0.02$; [d3] $P < 0.01$
[e] These controls were only 15 males and 7 females. Data are presented as means ± SE.

patients were classified according to Pak et al [2] into the following groups:

Dietary hypercalciuria (DH). (This correlated with absorptive hypercalciuria type II of Pak et al.) When their calciuria on a calcium restricted diet was below the upper limit of our controls, that is, 0.07 mmol/kg/day (<2.8 mg/kg/day), 18 patients could be included in this group.

Dietary calcium-independent hypercalciuria (IH). This was defined as patients who had calciuria still above 0.07 mmol/kg/day in spite of the calcium restricted diet. Actually this type of hypercalciuria was called "idiopathic" by Pak et al [2] and Coe and Bushinsky [6], even though these authors did not eliminate the patients with medullary sponge kidney (**Discussion**). Patients with IH were subsequently classified into: (1) absorptive hypercalciuria type I when fasting calciuria was lower than 0.33 mmol/mmol urinary creatinine (the upper limit of our controls) ($N = 8$ patients); (2) renal hypercalciuria when fasting calciuria was greater than 0.33 mmol/mmol urinary creatinine, whereas fasting PTH was elevated but decreased to normal after the calcium load; these criteria were fulfilled in only one patient with MSK. (3) The remaining 15 patients with fasting hypercalciuria and normal plasma PTH were classified in the undetermined hypercalciuria subgroup.

The number of previously formed Ca stones is in Table 3.

Measurement of vertebral mineral density

Vertebral mineral density (VMD) was determined using quantitative computerized tomodensitometry (CT). The measurement was performed in the third lumbar vertebra and used a calibration phantom [16, 17]. The calibration phantom is made of five tubes filled with progressively titrated solutions of K_2HPO_4. The regression line of the calibration test allows conversion between Hounsfield units and equivalent values of K_2HPO_4 expressed in mg/ml of spongious bone. The normal regression line of VMD related to age was determined for each sex in a group of 239 controls (106 males, 133 females). This regression line permits the results of our patients to be expressed in percent of the normal mean for age and sex.

Statistical analyses

Student's *t*-test and the non-parametric test of Wilcoxon for unpaired data were used to compare each parameter between the different groups and subgroups. The results are given as mean ± SEM.

In each group, linear correlations between various parameters were calculated by the least-squares method. When a significant correlation was observed, Spearman's rank correlation coefficient was determined to verify that the correlation was not skewed by extreme values.

Results

Urinary parameters

Calcium excretion. The 24 hour excretions of calcium were by selection in accordance with the criteria taken for the classification of the patients, that is, on free diet, higher in the two hypercalciuric groups than in controls; on calcium restricted diet, higher in the group with dietary calcium-independent hypercalciuria (IH) than in controls and in DH (Table 1).

Calciuria. In the IH group, fasting calciuria was higher than in controls and dietary hypercalciuria. By definition, fasting calciuria was normal in absorptive hypercalciuria type I (8 patients) and increased in the single patient with renal hypercalciuria. Fasting calciuria was increased in the group with undetermined hypercalciuria. This group of 15 patients repre-

Table 2. Fasting plasma phosphocalcic parameters

Plasma concentrations *N*	Controls 61 (12)	Dietary hypercalciuria 18	Idiopathic hypercalciuria 24	Idiopathic hypercalciuria: Absorptive hypercalciuria I 8	Idiopathic hypercalciuria: Renal hypercalciuria 1	Idiopathic hypercalciuria: Undetermined hypercalciuria 15
Calcium *mmol/liter*	2.40 ± 0.03	2.36 ± 0.02	2.38 ± 0.02	2.35 ± 0.04	2.35	2.37 ± 0.03
Phosphate *mmol/liter*	1.00 ± 0.03	1.01 ± 0.06	0.97 ± 0.02	0.91 ± 0.03	0.98	1.00 ± 0.03
Intact PTH *pg/ml*	38 ± 4	32 ± 4	32 ± 3	31 ± 5	74/42	28 ± 4
Gla protein *pg/ml*	6 ± 1	9 ± 1	8 ± 1	9 ± 1	12	8 ± 1
Alkaline *IU phosphatase*	135 ± 5	104 ± 7	101 ± 7	104 ± 11	102	99 ± 9
Calcidiol *ng/ml*	12 ± 1	14 ± 2	14 ± 1	14 ± 3	6	12 ± 1
Calcitriol *pg/ml*	50 ± 4	69 ± 5[a]	69 ± 5[c]	75 ± 6	58	67 ± 7

Data are presented as means ± SEM. The second figure of PTH for the patient with renal hypercalciuria is that measured 4 hours after the calcium load.

Significance of the comparisons:

Controls versus dietary hypercalciuria: [a] $P < 0.02$

Controls versus idiopathic hypercalciuria: [b] $P < 0.02$

sented the most important subtype of IH (60%), which explains why the whole group of IH had increased fasting calciuria.

After oral calcium load, calciuria in the IH group was significantly higher than in controls. This was due mainly to the subgroup with undetermined hypercalciuria which had a post calcium load calciuria greater than that of the group with absorptive hypercalciuria I. The increase of calciuria (ΔU_{Ca}) induced by the Ca load was also significantly higher in the IH group than in controls. It was comparable in dietary and idiopathic hypercalciuria as well as in the various subgroups of idiopathic hypercalciuria.

The urinary phosphate excretion on free diet was significantly higher in IH than in controls. No difference was observed between the two groups of hypercalciuric patients and between the three subgroups of IH. On Ca restricted diet, phosphaturia was greater in IH than in controls and in dietary hypercalciuria. No significant difference was observed between the three subtypes of dietary calcium-independent hypercalciuria. Fasting urinary phosphate was comparable in the 2 groups and in the controls.

Sodium excretion. The urinary excretion of sodium in the patients with DH and IH on free diet was higher than in controls. Sodium excretion was not different between the three subtypes of idiopathic hypercalciuria. On Ca restricted diet, that is, the day before the measurement of the fasting calciuria, no significant difference was observed in the sodium excretion between each group of patients and the controls, nor between the three subtypes of dietary calcium-independent hypercalciuria. This was true whether the sodium excretion was expressed per mmol of creatinine or as the absolute daily excretion (mean ± SEM for controls: 130 ± 11; DH: 148 ± 17; IH: 162 ± 18 mmol/24 hr; differences not significant). In the subgroups of IH mean ± SEM of natriuresis per 24 hours was 186 ± 37 for the absorptive hypercalciuria type I, 156 ± 20 for the undetermined hypercalciuria and 68 mmol for the renal hypercalciuric patients. The differences were not significant.

Total urea. The urinary excretion of urea on free and Ca restricted diets in patients with DH was comparable to that of controls and significantly lower than in patients with IH. No difference in urea excretion was observed between the three subtypes of IH.

THP. Total hydroxyprolinuria (THP) on Ca restricted diet was higher in patients with IH than in controls and in patients with DH. Fasting THP in the patients with IH was also higher than in controls but not higher than in patients with DH. No significant difference in THP was observed between the 3 subtypes of IH.

Plasma parameters

There was no significant difference between each group of patients and the controls as regards the plasma concentrations of calcium, phosphate, intact PTH, alkaline phosphatase, Gla-protein and calcidiol, nor the serum PTH concentrations (Table 2). Plasma calcitriol was significantly higher in the patients with DH and IH than in the controls. No significant difference was observed for all the plasma parameters between absorptive hypercalciuria type I and undetermined hypercalciuria. By definition, the only patient with renal hypercalciuria had elevated serum PTH which decreased to normal after the calcium load.

Clinical and vertebral mineral density data

Whereas there was no difference as regards the sex ratio and body weight between the various groups and subgroups of Ca stone formers (Table 3), the vertebral mineral density (VMD) was significantly lower in patients with IH (69 ± 4%) than in patients with DH (91 ± 6%) or in controls (100%). No significant difference in VMD was observed between the patients with undetermined hypercalciuria and those with absorptive hypercalciuria I. The single patient with renal hypercalciuria had a remarkable low VMD of 54%. Two other patients with fasting hypercalciuria of 0.34 and 0.68 mmol/mmol U_{Cr} had still lower VMD values at 50 and 35%.

Correlation studies

Table 4 summarizes only the significant correlations observed in the controls and in the two groups of hypercalciuric patients.

Controls. In the controls fasting calciuria was correlated to urea excretion on free diet ($U_{Ca}/U_{Cr} = 0.009 + 0.005\ U_{urea}/U_{Cr}$), but not on low calcium diet ($U_{Ca}/U_{Cr} = 0.057 + 0.004\ U_{urea}/U_{Cr}$). On free diets but not on low calcium diets, urea and phosphate excretions were correlated. No inverse correlation

Table 3. Clinical data and vertebral mineral density

Parameters	Controls	Dietary hypercalciuria	Idiopathic hypercalciuria	Idiopathic hypercalciuria		
				Absorptive hypercalciuria	Renal hypercalciuria	Undetermined hypercalciuria
N	61	18	24	8	1	15
Sex ratio *F/M*	20/41	6/12	7/17	1/7	0/1	6/9
Age *years*	35 ± 5	42 ± 5	45 ± 4	41 ± 3	56	49 ± 3
Body weight *kg*	70 ± 1.7	74 ± 3.5	71 ± 3	69 ± 4	63	72 ± 4
Prior calcium stone occurrence		2.5 ± 0.25	3.23 ± 0.5			
Vertebral mineral density *% of normal mean*	100 ± 10	91 ± 6	69 ± 4[b,c]	71 ± 4	54	68 ± 5

Data are presented as means ± SEM. The number of the controls for vertebral mineral density as 239 (106 males, 133 females).
Significance of the comparisons:
Controls versus dietary hypercalciuria: [a] none is significant
Controls versus idiopathic hypercalciuria: [b] $P < 0.01$
Dietary versus idiopathic hypercalciuria: [c] $P < 0.01$
Absorptive I versus undetermined hypercalciuria: [d] none is significant

Table 4. Significant correlation in the controls, dietary and idiopathic hypercalciuria

Group	First parameter	Second parameter	*N*	Least-squares		Spearman	
				r	*P*	r	*P*
Controls	U_{urea}(free diet)	U_{Ca}(fasting)	44	0.44	<0.01	0.41	<0.01
	U_{urea}(400 mg)	U_{Ca}(fasting)	44	0.26	<0.10	0.2	NS
	U_{urea}(free diet)	U_{PO_4}(free diet)	44	0.40	<0.01	0.4	<0.01
	U_{urea}(400 mg)	U_{PO_4}(400 mg)	44	0.25	<0.05	0.18	NS
	Plasma calcitriol	Plasma calcidiol	12	0.74	<0.01	0.70	<0.01
Dietary hypercalciuria	U_{urea}(free diet)	U_{PO_4}(free diet)	18	0.55	<0.03	0.52	<0.05
	U_{urea}(400 mg)	U_{PO_4}(400 mg)	18	0.62	<0.01	0.73	<0.01
Idiopathic hypercalciuria	U_{Ca}(free diet)	U_{urea}(free diet)	23	0.50	<0.01	0.47	<0.02
	U_{PO_4}(free diet)	U_{urea}(free diet)	23	0.50	<0.01	0.7	<0.01
	U_{Ca}(400 mg)	U_{urea}(400 mg)	23	0.58	<0.01	0.48	<0.02
	U_{PO_4}(400 mg)	U_{urea}(400 mg)	23	0.40	=0.05	0.46	=0.02
	U_{THP}(400 mg)	U_{urea}(free diet)	16	0.67	<0.01	0.49	<0.05
	U_{THP}(400 mg)	U_{urea}(400 mg)	16	0.49	<0.05	0.49	<0.05
	U_{THP}(fasting)	U_{urea}(400 mg)	15	0.50	<0.05	0.54	<0.05
	U_{Ca}(fasting)	U_{THP}(fasting)	15	0.69	<0.01	0.48	=0.05
	U_{Ca}(fasting)	U_{urea}(400 mg)	23	0.61	<0.01	0.41	<0.05
	U_{Ca}(fasting)	U_{urea}(free diet)	23	0.58	<0.01	0.4	=0.05
	U_{Ca}(fasting)	VMD L3	23	−0.28	=0.10	−0.37	=0.07
	Plasma calcitriol	VMD L3	23	0.50	<0.01	0.44	<0.05
	Plasma calcitriol	Fasting U_{Ca}	23	−0.41	<0.05	−0.45	<0.05
	Plasma calcitriol	Δ U_{Ca}(load)	23	0.65	<0.01	0.57	<0.01
	Plasma calcitriol	Plasma calcidiol	21	0.65	<0.01	0.56	<0.01
	Plasma calcitriol	Plasma PO_4	22[a]	−0.5	<0.01	−0.61	<0.01
	Plasma PTH	Plasma Gla protein	20	0.63	<0.01	0.24	NS
	Plasma PTH	U_{PO_4}fasting	23	0.46	<0.01	0.61	<0.01

Abbreviation is: VMD L3, vertebral mineral density of L3.
[a] The 2 patients with hypophosphatemia have been excluded

was found in healthy controls between fasting plasma phosphate and plasma calcitriol concentrations. A positive correlation between plasma calcidiol and plasma calcitriol has been found in this group of controls. Vertebral mineral density was not correlated with any biochemical parameters.

Hypercalciuria. In patients with dietary hypercalciuria, urea and phosphate excretions were correlated on both diets. No correlations was found in this group between plasma calcitriol and plasma or serum concentrations of phosphate, calcium, calcidiol, PTH and Gla protein. Vertebral mineral density was not correlated with any of the biochemical parameters.

In patients with dietary calcium independent hypercalciuria (IH), calcium and phosphate excretions were correlated with urea excretion on both diets. Hydroxyprolinuria on calcium restricted diet was correlated with urea excretion on both free and calcium restricted diets. Fasting hydroxyprolinuria was correlated to urea excretion on Ca restricted diet (2.1 + 0.93 U_{urea}; Fig. 1). Fasting calciuria was correlated to fasting hydroxyprolinuria (Fig. 2) as well as to urea excretion on free and calcium restricted diets. The slope of the regression line between fasting calciuria and urea excretion on free diet was five times steeper in IH than in the controls (0.024 vs. 0.005,

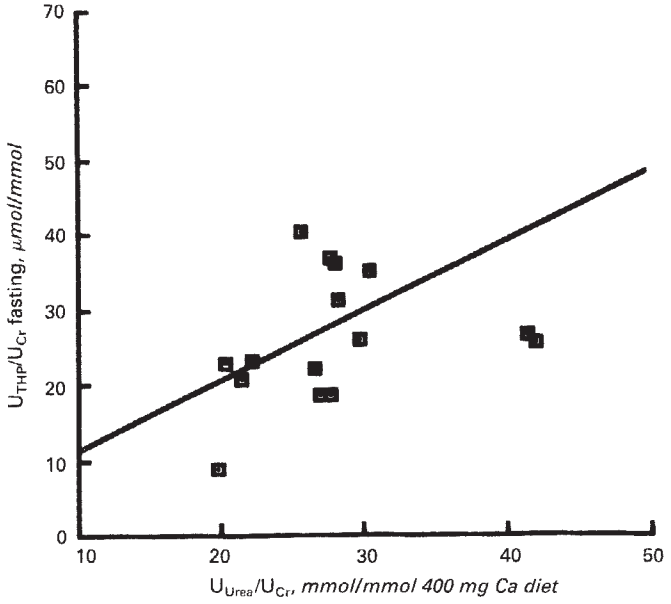

Fig. 1. *Correlation of fasting total hydroxyprolinuria with urea excretion on calcium restricted diet in patients with dietary calcium-independent hypercalciuria.* y = 2.1 + 0.93x; $r = 0.50$; $P < 0.05$.

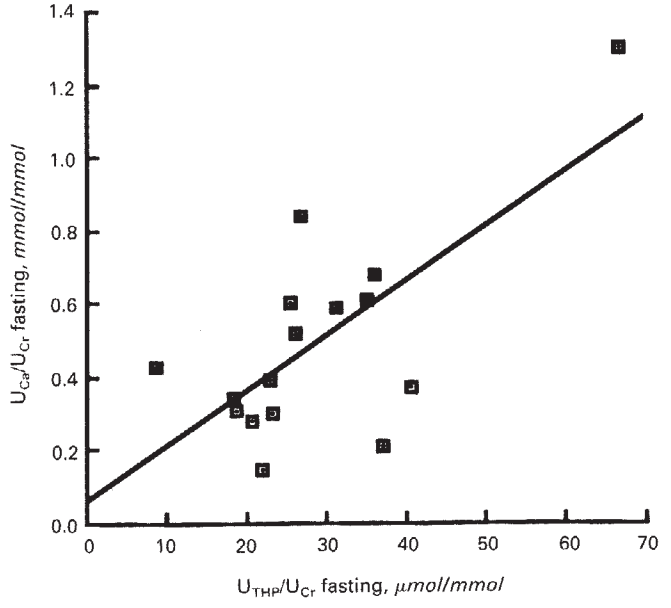

Fig. 2. *Correlation of fasting calciuria and fasting total hydroxyprolinuria in patients with dietary calcium-independent hypercalciuria.* y = 0.06 + 0.015x; $r = 0.69$; $P < 0.01$.

Fig. 3). No correlation between calcium and sodium excretion on free or Ca restricted diet was observed.

Vertebral mineral density was not correlated with fasting calciuria but was positively correlated with plasma calcitriol (Fig. 4). Vertebral mineral density was not correlated to hydroxyprolinuria nor to Gla protein.

Plasma calcitriol was negatively correlated to fasting calciuria (Fig. 5) and positively to the calciuria increase after the calcium load (an index of calcium absorption; Fig. 6). Plasma calcitriol

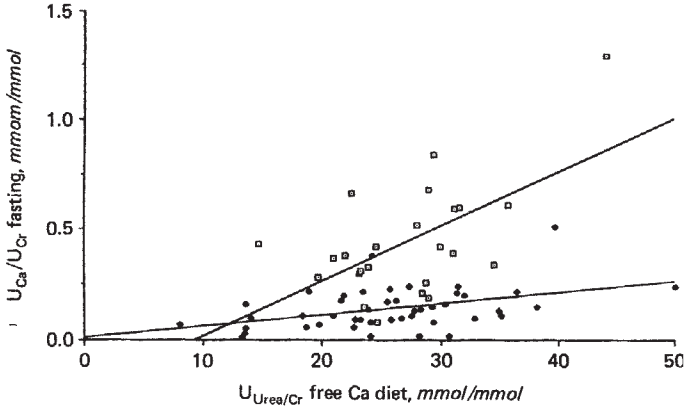

Fig. 3. *Comparison of the slopes of the regression line of fasting calciuria versus urea excretion on free diet in controls (◆, 0.005) and in patients with dietary calcium-independent hypercalciuria (□, 0.024).*

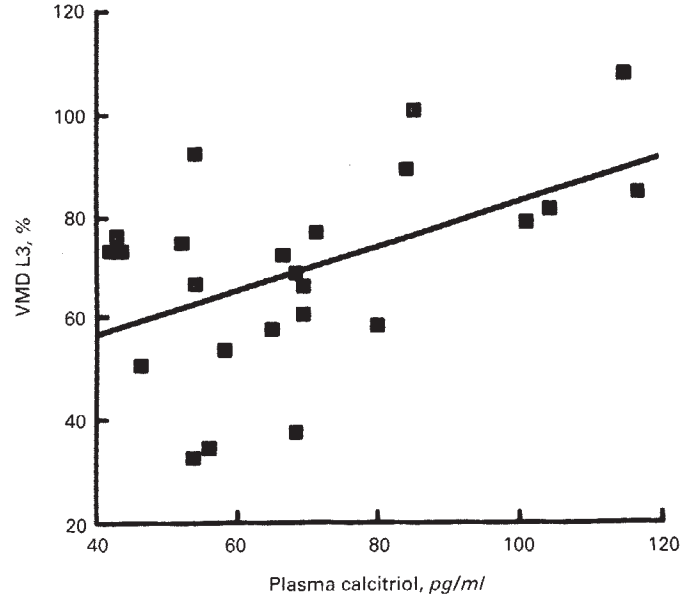

Fig. 4. *Correlation of vertebral mineral density with fasting plasma calcitriol in patients with dietary calcium-independent hypercalciuria.* y = 39 + 0.44x; $r = 0.50$; $P < 0.01$.

was also positively correlated to plasma calcidiol (Fig. 7) and negatively to plasma phosphate. The correlation between plasma PO_4 and plasma calcitriol has been confirmed after exclusion of two patients who had hypophosphatemia (patient 1, plasma PO_4 = 0.64 mmol/liter, plasma calcitriol = 101 pg/ml; patient 2, plasma PO_4 = 0.74 mmol/liter, plasma calcitriol = 115 pg/ml). The new correlation determined with 22 paired data is still significant ($P < 0.02$, $r = 0.5$, least squares method; $P < 0.01$, $r = 0.61$, Spearman's rank correlation coefficient; Fig. 8).

To exclude the role of decreased plasma calcidiol values in the correlation observed in IH between plasma calcidiol and plasma calcitriol, the correlation was again determined after exclusion of six patients with plasma calcidiol levels below the lower limit of normal (10 ng/ml). After exclusion of these patients the mean value (± SEM) for plasma calcidiol is 16.2 ± 1.2 ng/ml and the correlation between plasma calcidiol and

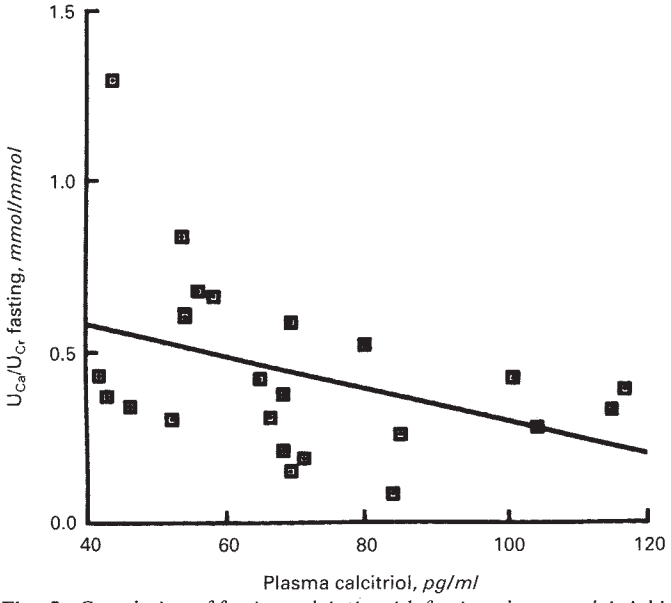

Fig. 5. *Correlation of fasting calciuria with fasting plasma calcitriol in patients with dietary-calcium independent hypercalciuria.* y = 0.77 − 0.005; $r = -0.41$; $P < 0.05$.

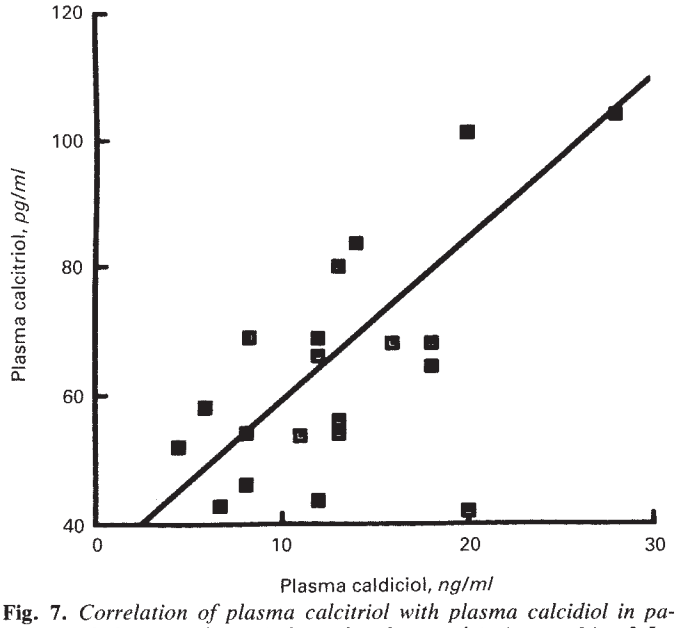

Fig. 7. *Correlation of plasma calcitriol with plasma calcidiol in patients with dietary calcium-independent hypercalciuria.* y = 34 + 2.5x; $r = 0.65$; $P < 0.01$.

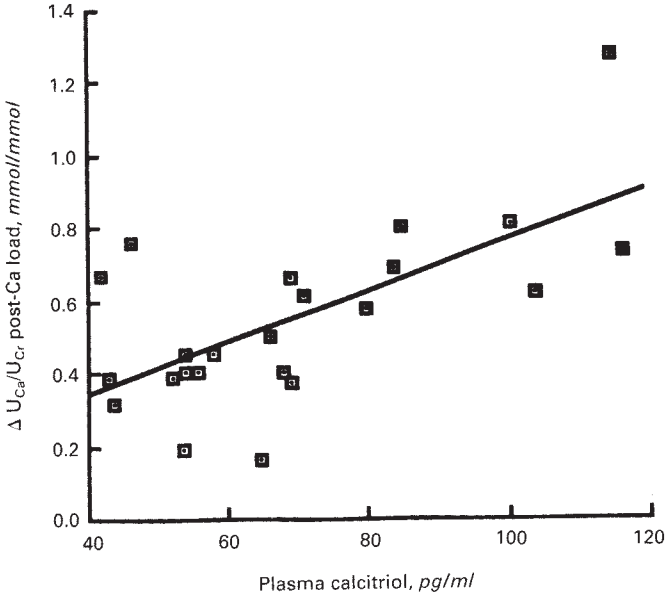

Fig. 6. *Correlation of calciuria increase after oral calcium load with fasting plasma calcitriol in patients with dietary calcium-independent hypercalciuria.* y = 0.06 + 0.007x; $r = 0.65$; $P < 0.01$.

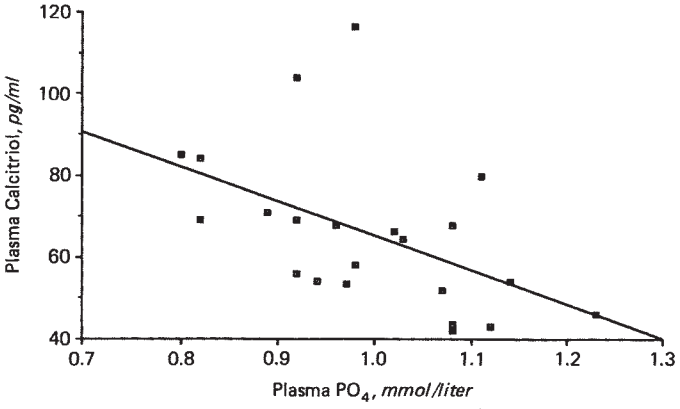

Fig. 8. *Correlation of plasma calcitriol with plasma phosphate in patients with dietary calcium-independent hypercalciuria and normophosphatemia.* y = 169 − 1.05x; $r = 0.50$; $P < 0.01$.

plasma calcitriol is still significant ($P = 0.01$, $r = 0.57$, least squares method; $P = 0.05$, $r = 0.5$ Spearman rank coefficient).

Serum PTH was not correlated to plasma calcitriol nor to fasting calciuria. Serum PTH was correlated to plasma Gla protein with the least squares method, but not with the Spearman's test.

Discussion

Bone density in hypercalciuric calcium stone formers

Vertebral mineral density was significantly decreased in calcium stone formers with hypercalciuria independent of calcium intake (IH) but not in those with dietary hypercalciuria. In patients with IH this density even reached the fracture threshold which corresponded to 70% of the normal mean. In fact, one patient in this group had a vertebral crush fracture.

Decrease in bone mineral density has already been reported in calcium stone formers by other authors using different techniques such as photonabsorptiometry of the distal radius [18] or of the lumbar spine [19], radiological densitometry of the proximal radial shaft [20], and in vivo neutron activation of the trunk and upper thighs [21]. However, in most of these studies insufficient data on the patients' calciuria and PTH levels were given. In two studies decreased bone mineral density was claimed to be present only in calcium stone formers with renal hypercalciuria, but this pathophysiological entity was actually proven by increased nephrogenic cAMP and/or increased PTH levels only in the study of Lawoyin et al [22] but not in that of

Lindergard et al [23]. In our study only one patient of the 24 with IH could be considered to have renal hypercalciuria. His vertebral mineral density was the third lowest of all the patients. Patients with absorptive hypercalciuria type I had a decreased mineral density of 71 ± 4%, that is, comparable to patients with undetermined fasting hypercalciuria (68 ± 5%) in spite of the fact that they had normal fasting calciuria.

Justification for the classification of hypercalciuria according to dietary calcium dependency, but not for further subclassification

The fact that the single patient with renal hypercalciuria had the third lowest VMD is in agreement with the data of Lawoyin et al and the primary pathophysiological mechanism proposed by Pak et al, namely the primary renal leak of calcium. However, its prevalence is very low: 1 out of 42 hypercalciuric calcium stone formers, that is, 2.4%. This makes the clinical relevance of this classification questionable.

The distinction between absorptive hypercalciuria type I and undetermined hypercalciuria according to the level of fasting calciuria does not appear to be justified by our data. Against making this distinction is the absence of difference in hydroxyprolinuria, in the vertebral mineral density and in the calciuria increase after oral calcium load, suggesting comparable absorption of calcium.

Since Muldowney, Freaney and Moloney [3] and Goldfarb [4] have shown that high sodium intake could increase fasting calciuria, it is interesting to note that this phenomenon could not explain the fasting hypercalciuria of the undetermined hypercalciuria subgroup, since the natriuresis of the previous day was not significantly different in the fasting hypercalciuric group than in the subgroup with absorptive hypercalciuria or in the controls. The absence of higher natriuresis in fasting hypercalciuria exists whether the calciuria is expressed per mmol of creatininuria or in absolute value per 24 hours. Thus it cannot be argued that the higher meat intake of calcium stone formers has led to higher creatinine excretion, which could explain that when the natriuresis is reported as a ratio on creatinine, it would be falsely diluted and therefore a higher sodium excretion would be masked in these patients.

Since Jaeger et al [24] have pointed out a high prevalence of obesity (40%) in patients with so-called idiopathic hypercalciuria and that the associated hyperinsulinism may be responsible of hypercalciuria, it is interesting to note that our population with dietary calcium independent hypercalciuria had comparable body weight to that of the controls, making it unlikely that hyperinsulinism is the main explanation for hypercalciuria.

Finally, it should be pointed out that only two patients had hypophosphatemia and could therefore enter the subgroup of absorptive hypercalciuria type III of Pak et al [2].

Therefore, we think with many authors [1, 5, 6] that the most clinically relevant distinction in hypercalciuric calcium stone formers is that of dietary hypercalciuria from the dietary calcium-independent hypercalciuria, that is, the usually called idiopathic hypercalciuria. This simple classification does not exclude, however, the role of other dietary factors such as salt, carbohydrates and, as it will be discussed later, animal protein intake.

Should the presence of medullary sponge kidney (MSK) be considered in the classification of hypercalciuria? This is a controversial issue. As a matter of fact, the presence of MSK is a well recognized risk factor of calcium lithiasis and should not point to patients having this abnormality as idiopathic calcium stone formers [10, 24]. However, the link between MSK and idiopathic (dietary calcium-independent) hypercalciuria, especially the renal hypercalciuria subtype, is not established for the following reasons: (1) hypercalciuria is inconstant in patients with MSK and its prevalence in these patients is not higher than in those without MSK (44% vs. 36% in the series of Parks et al [10]); (2) there is no agreement in the diagnosis criteria of MSK since authors like Parks et al [10] demand distinct radial linear striation or cystic collections of contrast medium in at least half of the papillae of both kidneys, whereas Jaeger et al [24] and Yendt, Jarzylo and Cohanim [25] consider that MSK is present when only one or two papillae are involved. (3) In contradiction with the presumed link between MSK and primary renal leak of calcium, the increase of serum PTH levels compatible with this diagnosis was quite inconstant since it was present in only 2 out of 11 patients of Yendt et al [25] in none of the six patients of Jaeger et al [24], and in 7 out of the 10 patients of Maschio et al [26] and in 3 of the 15 patients of O'Neill, Breslau and Pak [27]. Our three patients with MSK had dietary hypercalciuria in one case, dietary calcium independent hypercalciuria in two cases, of which only one had an actual renal hypercalciuria. It seems reasonable to discuss the pathophysiology of dietary calcium independent, that is, idiopathic, hypercalciuria at the exclusion of its relation to MSK.

Evidence for bone hyperresorption in dietary calcium-independent hypercalciuria (idiopathic hypercalciuria)

Besides decreased vertebral mineral density, our patients with idiopathic hypercalciuria were characterized by a fasting calciuria greater than in the controls and in the patients with dietary hypercalciuria, and by normal plasma concentrations of PTH, except in the single patient with renal hypercalciuria. Their fasting calciuria was correlated to fasting hydroxyprolinuria, suggesting that this hypercalciuria was linked to bone hyperresorption since hydroxyprolinuria is a known marker of bone resorption. Furthermore, fasting hydroxyprolinuria was higher in our IH patients than in controls. This has already been reported by others [9, 28, 29]. This abnormality together with results of calcium kinetics studies [30, 31] has led to the suggestion of increased bone resorption. These data also agree with the bone histological studies of Bordier, Ryckewaert and Gueris [32], who found increased osteoclastic surfaces accompanied by decreased osteoblastic surfaces in idiopathic hypercalciuric patients with normal or low plasma concentrations of PTH and phosphate, and of Steiniche et al [33] who found an increase in the resorption surfaces in 33 patients with idiopathic hypercalciuria, hypophosphatemia and normal PTH. In contrast to these reports, Malluche et al [34] found normal or decreased bone resorption associated with decreased bone formation and mineralization in patients with idiopathic hypercalciuria, but this latter was exclusively of the absorptive type I without fasting hypercalciuria. The fasting hypercalciuria of our patients could contributed to the decreased bone mass, although the negative correlation between fasting calciuria and

vertebral mineral density did not reach the level of significance ($P = 0.07$ only).

This increased bone resorption is not mediated by PTH since PTH levels were normal except in the single patient mentioned above. Increased plasma calcitriol concentration could theoretically contribute to fasting hypercalciuria because in fasting normal individuals on a calcium restricted diet, low dose of calcitriol has been proven to increase calciuria and to induce a negative calcium balance [35]. However this is not the case in our patients with idiopathic hypercalciuria, since their elevated plasma calcitriol was positively correlated to their vertebral mineral density and negatively correlated to fasting hypercalciuria. On the contrary, high plasma calcitriol in idiopathic hypercalciuria seems to have a protective effect for the skeleton by increasing the calcium absorption during the day; plasma calcitriol was correlated to the calciuria increase after a calcium load, that reflects calcium absorption. During the night, a primary bone hyperresorption would induce a primary release of skeletal calcium which may suppress calcitriol synthesis, explaining the negative correlation between fasting plasma calcitriol and fasting calciuria.

Although Broadus et al [36] and Adams et al [37] have shown that administration of calcitriol to healthy individuals could induce a fasting hypercalciuria due to increased intestinal absorption of calcium, the fasting hypercalciuria of our patients can not be explained by increased plasma calcitriol levels inducing a prolonged calcium absorption since: (a) there was no significant difference between undetermined hypercalciuria and absorptive hypercalciuria type I regarding the plasma calcitriol levels and the increase of calciuria after the oral calcium load; (b) a negative correlation, but not a positive one, was observed between plasma calcitriol and fasting calciuria. Even if fasting calciuria was not measured in our patients after administration of cellulose phosphate to cancel any question of intestinal calcium hyperabsorption, the fasting calciuria of our patients appears to originate mainly from bone resorption, since fasting calciuria was correlated to fasting hydroxyprolinuria in IH (RH patient being excluded).

Mechanisms of bone hyperresorption in idiopathic hypercalciuria

Two kinds of explanation may be proposed. The first one is an immunological one involving the monocyte. Pacific et al [29] have recently found an increased production of interleukin I by peripheral blood monocytes, associated with increased hydroxyprolinuria in calcium stone formers with fasting hypercalciuria. Interleukin I may indirectly induce bone resorption by stimulating prostaglandin bone resorption [38, 39]. This latter is known to be increased in idiopathic hypercalciuria and reduced by prostaglandin synthetase inhibition [40].

The second explanation is a nutritional one. High protein intake has been shown to favor osteoporosis [41] and hypercalciuria [24, 42–44], possibly by inducing a subtle metabolic acidosis [1, 45] as it increases the amount of amino acid sulfur oxidized to sulfate. This acidosis will release calcium salts from bone since these salts are used to buffer H^+ ions [45, 46]. It leads to an increase of the calcium filtered load and therefore to hypercalciuria, since tubular reabsorption of calcium is simultaneously decreased by a direct effect of acidosis as well as by the fact that sulfate in the tubular lumen is poorly reabsorbed and complexes calcium [1, 47]. In our patients with idiopathic hypercalciuria, urea excretion was significantly higher on a calcium restricted diet than in the controls, suggesting that their protein intake of non-dairy origin was greater. High protein catabolism could not explain this higher urea excretion because the patients' condition was excellent. Furthermore, the correlations between urea and calcium excretions were dramatic in this group of patients. Comparative to controls, the slope of the regression of fasting calciuria with urea excretion on free diet was five times steeper in the patients with idiopathic hypercalciuria, suggesting an increased sensitivity to the hypercalciuric action of dietary protein in this group. Such an increased sensitivity has been previously reported by Goldfard [4] in calcium stone formers regardless of their calciuria type. Finally urea excretion on calcium restricted diet was correlated to fasting hydroxyprolinuria and fasting calciuria whereas fasting calciuria correlated with fasting hydroxyprolinuria. Such correlations were not found in controls, suggesting that the patients with idiopathic hypercalciuria may be more sensitive to the resorptive effect of high protein intake that the controls. Since on calcium restricted diet the dairy products were excluded, the higher urea excretion observed on this diet in patients with idiopathic hypercalciuria suggests that their protein intake of non-dairy origin was higher. This high intake of animal protein actually increases calciuria simultaneously with hydroxyprolinuria and decreases urinary pH in calcium stone formers as this has been well demonstrated by Fellström et al [48]. The role of the acidosis induced by protein excess in the hypercalciuria of IH patients, however, is not predominant since it has been shown that at any given rate of renal net acid excretion, the calcium excretion is higher among patients with IH than in controls [49].

Disorder in the control of calcitriol synthesis in idiopathic hypercalciuria

In our patients with idiopathic hypercalciuria, fasting plasma calcitriol after four days of calcium restricted diet have been found elevated comparatively to controls. The mean value is 69 ± 5 pg/ml, a value very close to that found by Broadus et al [5, 50] (76 ± 10 pg/ml) in the same dietary conditions in his calcium stone formers with dietary independent hypercalciuria and increased calcium absorption after an oral calcium load. Increased plasma calcitriol level have also been reported in hypercalciuric Ca stone formers by other authors [51–54] with the exception of Coe et al [55], even with a very restricted calcium diet (<3.5 mmol/70 kg). These increased plasma levels of calcitriol have been proved to be in relation with increased synthesis not with decreased metabolic clearance [56].

What is remarkable in our patients is the negative correlation between plasma calcitriol and plasma phosphate although this latter remains in the normal range. This observation has been checked after exclusion of two patients with low plasma phosphate levels. Up to now this negative correlation between calcitriol and phosphate had been observed only in calcium stone formers with hypophosphatemia probably because of a primary renal leak of phosphate (absorptive hypercalciuria type III of Pak et al) [51, 52, 54–57]. This negative correlation is in accordance with the animal data showing that hypophos-

phatemia stimulates 25 (OH) vitamin $D_{1\alpha}$ hydroxylase by a growth hormone-dependent mechanism [58]. However, Portale et al [59] have reported that oral intake of phosphorus could inversely influence the production of calcitriol in humans in the absence of hypophosphatemia. Lower intakes of PO_4 are very unlikely in our patients since their PO_4 excretion on Ca restricted diet was higher than in controls in parallel with higher urea excretion, suggesting a higher intake of protein of non-dairy origin. Therefore the higher levels of calcitriol in our patients can not be explained by lower intakes of PO_4. A particular sensitivity of the 25 (OH) vitamin $D_{1\alpha}$ hydroxylase to plasma phosphate may therefore be postulated in our patients. This hypothesis is not supported by Insogna et al [60] who found that idiopathic hypercalciuric patients have a blunted response to their plasma calcitriol levels to the decrease of phosphate intake comparatively to normals. A negative correlation between plasma PO_4 and plasma calcitriol has also been reported in a Beduin tribe having members with asymptomatic hypercalciuria and only very mild hypophosphatemia (−1 SD of the mean of normal), besides members with hypophosphatemic rickets with hypercalciuria or members without any phosphocalcic abnormalities [61]. Since, with the exception of two patients all our patients with IH had normal plasma PO_4 and normal fasting urinary phosphate it is difficult to postulate that they had a mild form of phosphate renal leak.

The positive correlation between plasma calcitriol and plasma calcidiol is also unusual, since besides urolithiasis such a correlation has up to now only been reported in kidney transplant patients with renal failure [62], in elderly patients with primary hyperparathyroidism, mild renal insufficiency and vitamin D depletion [63], as well as in elderly normocalcemic subjects without primary hyperparathyroidism but with vitamin D depletion [64]. After exclusion of vitamin D depleted patients, this correlation holds true, which excludes vitamin D depletion as the primary explanation for this particular relationship between plasma calcidiol and plasma calcitriol in most of our patients. In normal vitamin D repleted man Bell et al [65] have shown that an increase in plasma 25 (OH) D induces a decrease in calcitriol production. In calcium stone formers, Varghese et al [66] have shown that, on the contrary, the increase of plasma 25 (OH) D (induced by ultraviolet B radiation) was associated with an increase in plasma calcitriol levels.

Thus vitamin D metabolism is characterized in idiopathic hypercalciuria by a disordered control of calcitriol synthesis. The nature and the site of this disturbed metabolism is unknown. Two explanations have been proposed by Lemann and Worcester [67]: activation of the renal 25 (OH) vitamin $D_{1\alpha}$ hydroxylase by an increased sensitivity of the enzyme to PTH or an occult extrarenal calcitriol synthesis in a granulomatous disorder like sarcoidosis [68]. This latter hypothesis may be put in relation with the abnormality of the monocytes observed in calcium stone formers with fasting hypercalciuria which have been proved to excessively secrete interleukin I [29]. As a matter of fact, interleukin I stimulates prostaglandin synthesis and prostaglandins have been proved to stimulate both bone resorption [40] and calcitriol synthesis [69]. Thus the two apparently contradictory phenomena that we have found in our patients with idiopathic hypercalciuria, namely the increased bone resorption leading to reduction of bone density and the protective effect of high plasma calcitriol levels, could be explained by abnormal monocytes.

Since in our patients we have a negative correlation between plasma calcitriol and plasma phosphate and a positive one between plasma calcitriol and plasma calcidiol, in spite of normal plasma phosphate and low or normal plasma calcidiol, but no correlation between plasma calcitriol and plasma PTH, we speculate that they have a hypersensitivity of their 25 (OH) vitamin $D_{1\alpha}$ hydroxylase to plasma PO_4, making calcitriol synthesis dependent on normal levels of 25 (OH) vitamin D.

Explanation of the normal vertebral mineral density in dietary hypercalciuria

The absence of decreased vertebral mineral density in spite of hypercalciuria may be explained by two nutritional factors: a higher intake of calcium and intake of non-dairy proteins lower than in patients with dietary calcium-independent hypercalciuria (IH). The higher calcium intake in this group is suggested by the normalization of calciuria when the patient has decreased his calcium intake. The lower intake of non-dairy protein in this group is suggested by the fact that urea excretion on calcium restricted diet (without dairy product) is lower than in IH patients. Furthermore, as in IH patients, the increased plasma concentration of calcitriol, may play also a protective effect by increasing calcium absorption. A potential hyperresorption due to increased levels of calcitriol is unlikely because of the normal hydroxyproline excretion.

Therapeutical implications

The fact that vertebral mineral density is decreased in calcium stone formers with dietary calcium-independent hypercalciuria but not in patients with dietary hypercalciuria militates against the formerly proposed restriction of dairy products in all calcium stone formers, a measure which is still very popular although its actual efficacy for prevention of lithiasis recurrence has never been proven [70]. As a matter of fact, this measure may have a deleterious effect on the bone of the patients by reducing their calcium intake, as it has been recently shown in calcium stone formers by Fuss et al [71], distal radius bone mineral content being significantly lower in those maintained on a low calcium diet for four years than in those maintained on a free diet. Therefore for all patients we recommend a normal calcium diet of 800 to 1000 mg and no dairy product restriction. Another reason for not restricting calcium intake is that this restriction increases oxaluria, which results in IH patients having an increase of the index of Robertson which evaluates the probability of being a stone former [72]. Therefore the only safe dietary measures advisable to reduce hypercalciuria are lower intakes of non-dairy protein, salt and excessive carbohydrates. When hypercalciuria persists in spite of these dietary measures, thiazides may be added since they reduce calciuria and have been proven independently to be capable of preventing both bone loss [73–75] and lithiasis recurrence [76, 77]. Prospective studies comparing thiazide therapy to placebo will be necessary to demonstrate their skeleton protective effect in calcium stone formers with idiopathic hypercalciuria.

Conclusions

(1.) Vertebral mineral density is decreased in calcium stone formers with dietary calcium independent hypercalciuria (IH)

but not in patients with dietary hypercalciuria. The distinction of these two groups of hypercalciuric patients is therefore clinically relevant.

(2.) The further distinction within IH of absorptive hypercalciuria type I (8 patients) from renal hypercalciuria (1 patient) is clinically more questionable, since 15 patients with fasting hypercalciuria and normal PTH remained unclassified, and because vertebral mineral density and biochemical parameters (at the exception of those taken for sub-classification) were comparable in absorptive hypercalciuria type I and undetermined fasting hypercalciuria.

(3.) A primary bone hyperresorption is the most likely explanation of most dietary calcium independent hypercalciuria, since (1) fasting hypercalciuria was correlated to fasting hydroxyprolinuria; (2) fasting hydroxyprolinuria was higher in IH than in controls; and (3) plasma concentrations of PTH are low normal, with exception of one case with renal hypercalciuria and medullary sponge kidney.

(4.) Bone resorption in IH was associated with and may be enhanced by a high protein intake of non-dairy origin, since fasting hypercalciuria and hydroxyprolinuria are correlated to urea excretion on a diet excluding dairy products.

(5.) Bone resorption in IH seems to be suppressed by high plasma calcitriol favoring calcium absorption, since plasma calcitriol is negatively correlated to fasting calciuria and positively correlated to vertebral mineral density and to the calciuria increase induced by a calcium load.

(6.) Calcitriol synthesis is disturbed in IH since plasma levels of calcitriol are elevated, whereas the plasma levels of calcidiol are normal, and plasma calcitriol is positively correlated to plasma calcidiol. Furthermore, in spite of normophosphatemia, plasma calcitriol is negatively correlated to plasma PO_4, suggesting a hypersensitivity of the 25 (OH) vitamin $D_{1\alpha}$ hydroxylase to plasma PO_4.

(7.) From a therapeutical point of view, these data suggest that exclusion of dairy products in hypercalciuric patients may be deleterious for their skeleton and that restriction of protein of non-dairy origin (especially meat) should be advised.

Acknowledgments. The authors thank Mrs. Martine Contard and Frank Dubal for preparing the manuscript, Mrs. N. Perrin, M. Lepoivre, M. Haye, N. Bontemps, A. Pecquet for technical help.

Reprint requests to Professor Albert Fournier, Centre Hospitalier Regional et Universitaire D'Amiens, Hôpital Sud Avenue Rene Laennec, Salouel, B.P. 3009-80030 Amiens Cedex, France.

References

1. LEMANN J: Idiopathic hypercalciuria, in *Nephrolithiasis*, edited by COE FL, BRENNER BM, STEIN J, New York, Churchill Livingstone, 1980, pp. 86–115
2. PAK CYC, BRITTON F, PETERSON R, WARD D, NORTHCOTT C, BRESLAU N, MACGUIRE J, NICAR M, NORMAN DA, PETERS P: Ambulatory evaluation of nephrolithiasis. Classification, clinical presentation and diagnostic criteria. *Am J Med* 69:19–30, 1980
3. MULDOWNEY FP, FREANEY R, MOLONEY MF: Importance of dietary sodium in the hypercalciuria syndrome. *Kidney Int* 22:292–296, 1982
4. GOLDFARB S: Dietary factors in the pathogenesis and prophylaxis of nephrolithiasis. *Kidney Int* 34:544–555, 1988
5. BROADUS AE, BURTIS WJ, OREN DA, SARTORI L, GAY L, ELLISON AF, INSOGNA KL: Concerning the pathogenesis of idiopathic hypercalciuria, in *Pathogenesis and Treatment of Nephrolithiasis*, edited by LINARI, MARANGELLA M, Contributions in Nephrology (vol 38) Basel, Karger, 1987, pp. 127–136
6. COE FL, BUSHINSKY DA: Pathophysiology of hypercalciuria. *Am J Physiol* 247:F1–F13, 1984
7. SUTTON RAL, WALKER VR: Responses to hydrochlorothiazide and acetazolamide in patients with calcium stones. *N Engl J Med* 302:709–713, 1980
8. BATAILLE P, BOUILLON R, FOURNIER A, RENAUD H, GUERIS J, IDRISSI A: Increased plasma concentrations of total and free $1,25(OH)_2D_3$ in calcium stone formers with idiopathic hypercalciuria, in *Pathogenesis and Treatment of Nephrolithiasis*, edited by LINARI F, MARANGELLA M, Contributions in Nephrology (vol 58), Basel, Karger, 1987, pp. 137–142
9. MESSA P, MIONI G, MONTANARO D, ADORATI M, ANTONUCCI F, FAVAZZA A, MESSA M, ENZMANN G, PAGANIN L, NARDINI R: About a primitive osseous origin of the so-called renal hypercalciuria, in *Pathogenesis and Treatment of Nephrolithiasis*, edited by LINARI F, MARAGELLA M, Contributions in Nephrology (vol 58), Basel, Karger, 1987, pp. 106–110
10. PARKS JH, COE FL, STRAUSS AL: Calcium nephrolithiasis and medullary sponge kidney in women. *N Engl J Med* 306:1088–1091, 1982
11. DELMAS P, SENNER D, WAHNER HW, MANN KG, RIGGS BL: Increase in serum bone σ carboxyglutamine acid protein with aging in women. Implications for the mechanism by the age-related bone loss. *J Clin Invest* 71:1316–1321, 1983
12. PREECE MA, O'RIORDAN JLH, LAWSON DEM, KODICEK E: A competitive protein binding assay for 25 hydroxycholecalciferol and 25 hydroxyergocalciferol in serum. *Clin Chem Act* 54:235–240, 1975
13. BOUILLON B, DE MOOR R, BAGGIOLINI EG, USKOKOVIC R: A radioimmunoassay for 1,25 dihydroxycholecalciferol. *Clin Chem* 26:562–567, 1980
14. KAO PC, JIANG NS, KLEE GG, PURNEL BC: Development and validation of a new radioimmunoassay for parathyrin (PTH). *Clin Chem* 28:69–71, 1982
15. GRANT RA: Estimation of hydroxyproline by the autoanalyzer. *J Clin Pathol* 17:685–686, 1964
16. CANN CE, GENANT HK: Precise measurement of vertebral mineral content using computed tomography. *J Comput Assist Tomograph* 4:493–500, 1980
17. LAVAL-JEANTET AM, MIRAVET L, BERGOT C, DE VERNEJOUL MC, KUNTZ D, LAVAL-JEANTET M: Tomodensitométrie vertébrale quantitative. Résultats sur 105 femmes consultant pour ostéoporose. *J Radiol* 68:495–502, 1987
18. ALHAVA EM, JUUTI M, KARJALAINEN P: Bone mineral density in patients with urolithiasis. *Scand J Urol Nephrol* 10:154–156, 1976
19. MALVASI L, SARTORI L, GIANNINI S, AL AWADY M, MUSAIO F, VAROTTO S, D'ANGELO A: Mineral metabolism and bone mineral content in calcium nephrolithiasis with and without hyperparathyroidism. (abstract) *Urol Res* 16:190, 1988
20. VELENTZAS C, OREOPOULOS DG, MEEMA S, MEEMA HE, NUTSUGA T, ALISON E, KATIRTZOGLOU A, CRASSWELLER P: Dietary calcium restriction may be good for patients' stones but not for their bones, in *Urolithiasis Clinical and Basic Research*, edited by SMITH, ROBERTSON, FINLAYSON, New York, Plenum Press, 1981, pp. 847–854
21. BARKIN J, WILSON DR, MANUEL MA, BAYLEY A, MURRAY T, HARRISON J: Bone mineral content in idiopathic calcium nephrolithiasis. *Miner Electrol Metab* 11:19–24, 1985
22. LAWOYIN S, SISMILICH S, BROWNE B, PAK CYC: Bone mineral content in patients with calcium urolithiasis. *Metabolism* 28:1250–1254, 1979
23. LINDERGARD B, COLLEEN S, MANSSON W, RADEMARK C, ROGLAND B: Calcium loading test and bone disease in patients with urolithiasis. *Proc EDTA* 20:460–465, 1983
24. JAEGER P, PORTMANN L, GINALSKI JM, CAMPICHE M, BURCKHARD P: Dietary factors and medullary sponge kidneys as causes of the so-called idiopathic renal leak of calcium. *Am J Nephrol* 7:257–263, 1987
25. YENDT ER, JARZYLO S, COHANIM M: Medullary sponge kidney, in *Urolithiasis*, edited by WALKER VR, SUTTON RAL, CAMERON

ECB, PAK CYC, ROBERTSON WG, New York, Plenum Press, 1989, pp. 383–388
26. MASCHIO G, TESSITORE N, D'ANGELO A, FABRIS A, CORGNATI A, OLDRIZZI L: Medullary sponge kidney and hyperparathyroidism: A puzzling association. *Am J Nephrol* 2:77–84, 1982
27. O'NEILL M, BRESLAU NA, PAK CY: Metabolic evaluation of nephrolithiasis in patients with medullary sponge kidney. *J Am Med Assoc* 245:1233–1236, 1981
28. SUTTON RAL, WALKER VR: Bone resportion and hypercalciuria in calcium stone formers. *Metabolism* 35:485–488, 1986
29. PACIFI R, ROTHSTEIN M, RIFAS L, LAU KHW, BAYLINK DG, AVIOLI LV, HRUSKA K: Increased monocyte interleukin-I activity and decreased vertebral bone density in patients with fasting hypercalciuria. *J Clin Endocrinol Metab* 71:138–145, 1990
30. LIBERMAN UA, SPERLING O, ATSMON A: Metabolic and calcium kinetic studies in idiopathic hypercalciuria. *J Clin Invest* 47:2580–2590, 1969
31. ANDERSON J, LEE HA, TOMLINSON RWS: Some metabolic aspects of idiopathic hypercalciuria. *Nephron* 4:129–138, 1976
32. BORDIER P, RYCKEWART A, GUERIS J: On the pathogenesis of so-called hypercalciuria. *Am J Med* 63:398–409, 1977
33. STEINICHE T, MOSEKILDE L, CHRISTENSEN MS, MELSEN F: A histomorphometric determination of iliac bone remodeling in patients with recurrent renal stone formation and idiopathic hypercalciuria. *APMIS* 4:309–316, 1989
34. MALLUCHE HH, TSCHOEPPE W, RITZ E, MEYER-SABELLEK W, MASSRY SG: Abnormal bone histology in idiopathic hypercalciuria. *J Clin Endocrinol Metab* 50:654–658, 1980
35. MAIERHOFER WJ, GRAY RW, CHEUNG HS, LEMANN J JR: Bone resorption stimulated by elevated serum 1,25 $(OH)_2$ vitamin D concentrations in healthy man. *Kidney Int* 24:555–566, 1983
36. BROADUS AE, ERICKSON JB, GERTNER JM, COOPER K, DOBBINS JW: An experimental human model of 1,25 $(OH)_2$ D mediated hypercalciuria. *J Clin Endocrinol Metab* 59:202–206, 1984
37. ADAMS ND, GRAY RW, LEMAN J, CHEUNG HS: Effects of calcitriol administration on calcium metabolism in healthy man. *Kidney Int* 21:90–97, 1982
38. GOWEN M, MEIKLE MC, REYNOLDS JJ: Stimulation of bone resorption in vitro by a non-prostanoid factor released by human monocytes in culture. *Biochem Biophys Acta* 762:471–474, 1983
39. TASHJIAN AH, VOEIKE EF, LAZZARO M, SINGER FR, ROBERTS NB, DERYNCK R, WINKLER ME, LEVIN L: α and β human transforming growth factors stimulate prostaglandin production and bone resorption in cultured mouse calvaria. *Proc Natl Acad Sci USA* 82:4535–4538, 1985
40. FILIPPONI P, MANNARELLI C, PACIFI R, GROSSI E, MORETTI I, TINI S, CARLONI C, BLASS A, MORUCCI P, HRUSKA KA, AVIOLI LV: Evidence for a prostaglandin-mediated bone resorptive mechanism in subjects with fasting hypercalciuria. *Cal Tissue Int* 43:61–66, 1988
41. WACHMAN A, BERNSTEIN DS: Diet and osteoporosis. *Lancet* i:958–959, 1968
42. ALLEN LH, ODDOYE EA, MARGEN S: Protein induced hypercalciuria: A longer term study. *Am J Clin Nutr* 32:741–749, 1979
43. LICATA A, BOU E, BARTTER FC, COX J: Effects of dietary protein on urinary calcium in normal subjects and in patients with nephrolithiasis. *Metabolism* 28:895–900, 1979
44. WALKER RM, LINKSWILER HM: Calcium retention in the adult human male as affected by protein intake. *J Nutr* 102:1297–1302, 1972
45. LEMANN J JR, LITZOW JR, LENNON EJ: The effects of chronic acid loads in normal man: Further evidence for the participation of bone mineral in the defense against chronic metabolic acidosis. *J Clin Invest* 45:1608–1614, 1966
46. DELLING G, DONATH K: Morphometrische, elecktronenmikroskopische und physikalisch-chemische Untersuchungen über die experimentelle Osteoporose bei chronischer Acidose. *Virchow Arch* 358:321–330, 1973
47. ALLEN LH, BARTLETT RS, BLOCK GD: Reduction of renal calcium reabsorption in man by consumption of dietary protein. *J Nutr* 109:1345–1350, 1979
48. FELLSTRÖM B, DANIELSON BG, KARLSTRÖM B, LITHELL H, LJUNGHALL S, VESSBY B, WIDE L: Effects of high intake of dietary animal protein on mineral metabolism and urinary supersaturation of calcium oxalate in renal stone formers. *Br J Urol* 56:263–269, 1986
49. LEMANN J: Urinary calcium excretion and net acid excretion: Effects of dietary protein, carbohydrate and calories, in *Urolithiasis and Related Clinical Research*, edited by SCHWILLE PO, SMITH LH, ROBERTSON WG, VAHLENSIECK W, New York, Plenum Press, 1985, pp. 53–60
50. BROADUS AE, INSOGNA KI, LANG R, ELLISON AF, DREYER BE: Evidence for disordered control of 1,25 dihydroxyvitamin D production in absorptive hypercalciuria. *N Engl J Med* 311:73–80, 1984
51. SHEN FH, BAYLINK DJ, NIELSEN RL, SHERARD DJ, IVEY JL, HAUSSLER MR: Increased serum 1,25 dihydroxyvitamin D in idiopathic hypercalciuria. *J Lab Clin Med* 90:955–962, 1977
52. GRAY RW, WILZ DR, CALDAS AE, LEMANN J: The importance of phosphate in regulating plasma 1,25 $(OH)_2$ vitamin D levels in humans: Studies in healthy subjects, in calcium-stone formers and in patients with primary hyperparathyroidism. *J Clin Endocrinol Metab* 45:299–306, 1977
53. KAPLAN RA, HAUSSLER MR, DEFTOS LJ, BONE H, PAK CYC: The role of 1,25 dihydroxyvitamin D in the mediation of intestinal hyperabsorption of calcium in primary hyperparathyroidism and absorptive hypercalciuria. *J Clin Invest* 59:756–760, 1977
54. ZERWEKH M, PAK CYC: Selective effects of thiazide therapy on serum 1α, 25-dihydroxyvitamin D and intestinal calcium absorption in renal and absorptive hypercalciurias. *Metabolism* 24:13–17, 1980
55. COE FL, FAVUS MJ, CROCKETT T, STRAUSS AL, PARKS JH, PORAT A, GANT TC, SHERWOOD LM: Effects of low-calcium diet on urine calcium excretion, parathyroid function and serum 1,25 $(OH)_2$ D_3 levels in patients with idiopathic hypercalciuria and in normal subjects. *Am J Med* 72:25–32, 1982
56. ISOGNA KL, BROADUS AE, DREVER BE, ELLISON AF, GERTNER JM: Elevated production rate for 1,25 dihydroxyvitamin D in patients with absorptive hypercalciuria. *J Clin Endocrinol Metab* 61:490–495, 1985
57. BROADUS AE, INSOGNA KL, LANG R, MALLETTE LE, OAEN DA, KLIGER AS, ELLISON AF: A consideration of the hormonal basis and phosphate leak hypothesis of absorptive hypercalciuria. *J Clin Endocrinol Metab* 58:161–161, 1984
58. GRAY RW, GARTHWAITE TL: Activation of renal 1,25 dihydroxyvitamin D_3 synthesis by phosphate deprivation: Evidence for a role of growth hormone. *Endocrinology* 116:189–193, 1985
59. PORTALE AA, HALLORAN BP, MURPHY MM, MORRIS RCJ: Oral intake of phosphorus can determine the serum concentration of 1,25 dihydroxyvitamin D by determining its production rate in humans. *J Clin Invest* 77:7–12, 1986
60. INSOGNA K, LANG R, ELLISON A, BROADUS A: Qualitative abnormality in 1,25 dihydroxy vitamin D response to phosphorus deprivation in patients with absorptive hypercalciuria. (abstract) *Clin Res* 33:433A, 1986
61. TIEDER M, MODAI D, SHAKED U, SAMUEL R, LIBERMAN UA: Idiopathic hypercalciuria and hereditary hypophosphatemic rickets. Two phenotypical expressions of a common genetic defect. *N Engl J Med* 316:125–129, 1987
62. LUCAS PA, WOODHEAD J, BROWN RC: Vitamin D_3 metabolites in chronic renal failure and after renal transplantation. *Nephrol Dial Transpl* 3:70–76, 1988
63. PATRON P, GARDIN JP, PAILLARD M: Renal mass and reserve of vitamin D: Determinants in primary hyperparathyroidism. *Kidney Int* 31:1174–1180, 1987
64. BOUILLON R, AUWERX JH, LISSENS WD, PELEMANS W: Vitamin D status in the elderly: Seasonal substrate deficiency causes 1,25 dihydroxycholecalciferol deficiency. *Am J Clin Nutr* 45:755–763, 1987
65. BELL NH, GREENE V, SHARRY J, SHAW J: Evidence that 25-hydroxyvitamin D has a role in the regulation of calcium metabolism in man. (abstract) *J Bone Miner Res* 1(Suppl):380, 1986
66. VARGHESE M, RODMAN JS, WILLIAMS GG, BROWN A, CARTER DM, ZERWEKH JE, PAK CYC: The effect of ultraviolet B radiation treatments on calcium excretion and vitamin D metabolites in kidney stone formers. *Clin Nephrol* 31:225–231, 1989
67. LEMANN JJ, WORCESTER AM: Nephrolithiasis, in *Textbook of Nephrology*, edited by MASSRY SG, GLASSOCK RJ, Baltimore, Williams and Wilkins, 1989, pp. 920–941
68. SANDLER LM, WINEARLS CG, FRAHER LJ, CLEMENS TL, SMITH R, O'RIORDAN JLH: Studies of the hypercalcemia of sarcoidosis: Effect of steroids and exogenous vitamin D_3 on the circulating

concentrations of 1,25 dihydroxyvitamin D_3. *Quart J Med* (New Series) 53:165–180, 1984

69. WARK JD, LARKINS RG, EISMAN JA, MARTIN TJ: Prostaglandins and 25 hydroxy vitamin $D_{1\alpha}$ hydroxylase, in *Vitamin D, Basic Research and its Clinical Application*, edited by NORMAN AN, Berlin, Walter de Gruyter, 1977, pp. 563–566
70. NORDIN BEC, BANY H, BALASA L: Dietary treatment of recurrent calcium stone disease, in *Urinary Calculi*, edited by DELATTE LC, RAPADO A, HODGKINSON A, Basel, Karger, 1973, pp. 170–176
71. FUSS M, PEPERSACK T, VANGEEL J, CORVILAIN J, VANDEWALLE JC, BERGMAN P, SIMON J: Involvement of low-calcium diet in the reduced bone mineral content of idiopathic renal stone formers. *Calcif Tissue Int* 46:9–13, 1990
72. BATAILLE P, CHARRANSOL G, GREGOIRE I, FOURNIER A: Effect of calcium restriction on renal excretion of oxalate and the probability of being a stone former. *J Urol* 130:218–221, 1983
73. COE FL, PARKS JH, BUSHINSKY DA, LANGMAN CB, FAVUS MJ: Chlorthalidone promotes mineral retention in patients with idiopathic hypercalciuria. *Kidney Int* 33:1140–1146, 1988
74. WASNICH RD, BENFANTE RJ, YANO K, HEILBRUN L, VOGEL JM: Thiazide effect on the mineral content of bone. *N Engl J Med* 309:344–347, 1983
75. RAY WA, GRIFFIN MR, DOWNEY W, MELTON LJ: Long term use of thiazide diuretics and risk of hip fracture. *Lancet* i:687–690, 1989
76. LAERUM E, LARSEN S: Thiazide prophylaxis of urolithiasis: A double-blind study in general practice. *Act Med Scand* 215:383–389, 1984
77. ETTINGER B, CITRON JT, TANG A, LIVERMORE B: Prophylaxis of calcium oxalate stones; clinical trials of allopurinol, magnesium hydroxide and chlorthalidone, in *Urolithiasis and Related Clinical Research*, edited by SCHWILLE, SMITH, ROBERTSON, VAHLENSIECK, New York, Plenum Press, 1985, pp. 549–553